

## Treatment of Cancers

The present invention relates to the treatment of cancers.

US Patent 5,089,273 relates to compounds identified as ecteinascidins. In particular, it relates to ecteinascidins 729, 743, 759A, 759B and 770. The compounds are disclosed to have antibacterial properties and some are also useful as antitumor agents.

We have now found that ecteinascidin 743 has exceptional activity in the treatment of sarcomas and mesotheliomas. A sarcoma is a cancer arising from connective tissue such as muscle or bone. A mesothelioma is a tumour of the mesothelium of the pleura, pericardium or peritoneum.

Thus, the present invention provides a method of treating any mammal, notably a human, affected by a sarcoma or mesothelioma which comprises administering to the affected individual a therapeutically effective amount of ecteinascidin 743, or a pharmaceutical composition thereof. Examples of human sarcomas to be treated include osteosarcomas and soft tissue sarcomas, leiomyosarcomas, fibrosarcomas and mesotheliomas.

The present invention also relates to pharmaceutical preparations, which contain as active ingredient ecteinascidin 743, as well as the processes for its preparation.

Examples of pharmaceutical compositions include any solid (tablets, pills, capsules, granules, etc.) or liquid (solutions, suspensions or emulsions) with suitable composition or oral, topical or parenteral administration, and they may contain the pure compound or in combination with any carrier or other pharmacologically active compounds. These compositions may need to be sterile when administered parenterally.

Administration of the composition of the present invention may be by any suitable method, such as intravenous infusion, oral preparations, intraperitoneal and intravenous administration. Intravenous delivery may be carried out over any suitable time period, such

as 12 to 24 hours or even longer if required, at suitable intervals of say 2 to 4 weeks.

Pharmaceutical compositions containing ecteinascidin 743 may be delivered by liposome or nanosphere encapsulation, in sustained release formulations or by other standard delivery means.

The correct dosage of ecteinascidin 743 of this invention will vary according to the particular formulation, the mode of application, and the particular *situs*, host and tumour being treated. Other factors like age, body weight, sex, diet, time of administration, rate of excretion, condition of the host, drug combinations, reaction sensitivities and severity of the disease shall be taken into account. Administration can be carried out continuously or periodically within the maximum tolerated dose.

The compositions of this invention may be used with other drugs to provide a combination therapy. The other drugs may form part of the same composition, or be provided as a separate composition for administration at the same time or a different time. The identity of the other drug is not particularly limited, and suitable candidates include:

- a) drugs with antimetabolic effects, especially those which target cytoskeletal elements, including microtubule modulators such as taxane drugs (such as taxol, paclitaxel, taxotere, docetaxel), podophylotoxins or vinca alkaloids (vincristine, vinblastine);
- b) antimetabolite drugs such as 5-fluorouracil, cytarabine, gemcitabine, purine analogues such as pentostatin, methotrexate);
- c) alkylating agents such as nitrogen mustards (such as cyclophosphamide or ifosfamide);
- d) drugs which target DNA such as the anthracycline drugs adriamycin, doxorubicin, pharmorubicin or epirubicin;
- e) drugs which target topoisomerases such as etoposide;
- f) hormones and hormone agonists or antagonists such as estrogens, antiestrogens (tamoxifen and related compounds) and androgens, flutamide, leuporelin, goserelin, cypotrone or octreotide;
- g) drugs which target signal transduction in tumour cells including antibody derivatives such as herceptin;

- h) alkylating drugs such as platinum drugs (cis-platin, carboplatin, oxaliplatin, paraplatin) or nitrosoureas;
- i) drugs potentially affecting metastasis of tumours such as matrix metalloproteinase inhibitors;
- j) gene therapy and antisense agents;
- k) antibody therapeutics; and
- l) other bioactive compounds of marine origin, notably the didemnins such as aplidine.

The present invention also extends to the compounds for use in a method of treatment, and to the use of the compounds in the preparation of a composition for treatment of cancer.

#### Example

Eleven patients (9 soft tissue sarcomas and 2 osteosarcomas) received ET-743, 10 at a dose of  $1500 \mu\text{g}/\text{m}^2$  and one at the maximum tolerated dose of  $1800 \mu\text{g}/\text{m}^2$ . Nine were treated in a phase I clinical trial, while two received ET-743 on a compassionate use basis. Sex 6 men/5 women; median age 37 years (16 to 71); median number of previous chemotherapy regimes 2 (1 to 4), all patients pretreated with anthracyclines and alkylators; median PS 1 (0 to 2); median number of metastatic sites 2 (1 to 3).

Et-743 was administered by 24 hours continuous infusion every three weeks, over 38 cycles.

Two partial responses were obtained, one lasting over four months, two minor responses, and three stabilisations lasting over four months. Among the two osteosarcomas, there was one partial response and one minor response, both still ongoing (WHO criteria).